1

Past, Current and Future Clinical Applications of MEG

Garreth Prendergast and Mark Hymers
York Neuroimaging Centre, University of York
United Kingdom

1. Introduction

Magnetoencephalography (MEG) is a technique which detects weak magnetic fields from above the surface of the head produced by electrical activity within the brain (Hämäläinen et al., 1993). It is non-invasive, acoustically silent and able to measure a direct correlate of neuronal activity with sub-millisecond resolution. The technique is therefore well suited to clinical applications as it can readily be used in children and other populations who may not tolerate more demanding procedures such as fMRI or PET. Clinical applications of MEG, although currently limited, have developed in parallel with advances in hardware, software, analysis tools and general understanding of the technique as a non-invasive measure of biomagnetic neuronal activity. The goal of this review is to describe the advances made to date regarding the clinical applications of the technique and the potential areas for expansion and application in the future.

Although much MEG research has been conducted in clinical populations, helping to provide an understanding of the pathology and manifestation of various categories of illness, it generally remains a technique used in the research laboratory rather than as a routine part of clinical evaluations. MEG is routinely used in research to investigate the dynamic neuronal processes involved in the representation of sensory systems such as vision, audition, somatosensation and movement. The technique is also readily applied to experiments studying more cognitive processes such as language perception, memory encoding and retrieval and higher level tasks. Non-invasive imaging of the human brain is potentially a very useful diagnostic tool in the identification, prevention and treatment of numerous disease and illnesses as it is able to study a range of cerebral functions.

The main clinical application of MEG remains in the pre-surgical evaluation of patients suffering from epilepsy. In recent years, the technique has been applied to the study of a much broader range of symptoms and pathologies, however this is almost exclusively in the context of research on clinical populations rather than being a routinely used diagnostic procedure. The aim of this chapter is not to provide an exhaustive review of all studies which report the use of MEG scanning techniques on individuals from a clinical population. The aim is to give an overview of how the clinical applications of the technique have developed in parallel with purely methodological and empirical research applications and to highlight steps which are necessary for the technique to be more readily applied to a wider range of clinically relevant problems. The first part of this chapter gives on overview of the early uses of MEG in the patient care and treatment plan of individuals suffering from epilepsy. Again, rather than focusing on the many studies published in this area which provide evidence for

the usefulness of MEG as a diagnostic tool, the chapter will focus on describing how the use of MEG in the epilepsy field has continued to evolve and develop in conjunction with the methodological and cognitive applications of the technique. In many ways, the use of MEG in the epilepsy population represents a bench-mark for what may be possible in other clinical populations. The chapter will then describe preliminary results from patient groups suffering from a range of diseases including Parkinsonism, Alzheimer's disease, cortical lesions, and Autism. The main theme of the chapter will be that it is essential that high-quality, robust and rigorous research studies precede any advances towards using MEG as a clinically useful tool and that these studies must be performed by multi-disciplinary research teams combining methodological and technical expertise with clinicians willing to strive towards faster, more objective and robust diagnostic methods. The chapter concludes that, although currently the application of MEG as a diagnostic tool to many types of illness is premature, the potential uses of MEG as a clinically accessible technique are vast. Due to large steps forward in the understanding of MEG signals and the proliferation of specific and flexible analysis techniques, the effectiveness of MEG now extends far beyond that of epilepsy and the next 5-10 years could see MEG become a diagnostic tool for a great many conditions.

2. Epilepsy research

Epileptic seizures are caused by spontaneous and uncontrolled electrical activity within the brain. Although there are many different sub-types of epilepsy, many of these manifest themselves as spontaneous, high-amplitude electrical activity and therefore are particularly well suited to detection via MEG. There are a number of excellent reviews of the role of MEG in the diagnosis and pre-surgical evaluation of epilepsy patients (for example da Silva, 2005; Knowlton, 2003; Tovar-Spinoza et al., 2008). As outlined in the introduction, the aim of this chapter is not to exhaustively describe the evidence for the effectiveness of MEG in the diagnosis of epilepsy, but to outline the progression of the analyses and methods used in the study of epilepsy and to highlight where this has been successful.

2.1 Early epilepsy research

Initial studies utilising MEG to measure magnetic field distributions from epilepsy patients treated the technique as a subtle variation on electroencepahlography (EEG). EEG has been a widely used technique with which to categorise various types of epilepsy and to determine the best course of treatment for a given pathology for many decades (Abbott & Schwab, 1948; Parker, 1947). EEG is still the most commonly used tool in hospitals to determine the focus of an individuals epilepsy. Initially MEG was used in a similar way, with the magnetic fields being analysed in much the same way as the EEG waveforms. The standard method was to visualise the waveforms on the electrodes or sensors and describe the scalp locations which showed slow, or spike-wave activity. Rose et al. (1987) used MEG, EEG and electrocorticography to measure inter-ictal spikes from three young adults suffering from epilepsy. It was found that MEG dipoles could be calculated from the scalp topography and a simple dipole fitting algorithm localised these to the anterior-temporal lobe. This localisation showed good concordance with the intra-operative electrode recordings from various surfaces of the temporal lobe, whereas the mapping of EEG spikes showed a localisation either anterior or posterior to the location identified by MEG. This was one of the first examples of a case where the localisation of high-amplitude inter-ictal activity in MEG not only appeared possible, but was also more closely related to the data collected by electrodes placed on the cortical surface during neurosurgery than the localisation achieved via EEG.

Following these early studies there were a number of validatory experiments which compared the localisation capabilities of MEG to those of EEG and intra-operative recordings (for example Knake et al., 2006; Rose et al., 1991). The consensus was that MEG provided a viable alternative to the invasive procedure of electrocorticography for pre-surgical localisation of epileptogenic zones and, due to the spatial smearing of electrical signals caused by the conductivity of the dura and skull, MEG provided a potentially more reliable and accurate signal than EEG on which to base the localisation of epileptiform activity (Nakasato et al., 1994). The primary analysis tool for analysing these high-amplitude, transient bursts of energy was the equivalent current dipole (ECD). Ebersole (1997) provides an introduction to the concept and implementation of dipole models to epilepsy data, but the technique is simply a fitting procedure in which an algorithm determines the location, orientation and strength of a dipole which minimises the error between the observed field and the field topography produced by the model. The head is assumed to be a sphere and the ECDs calculated are typically considered valid if the correlation between the modelled and observed field patterns is greater than 98% and have a physiologically realistic magnitude (Otsubo & Snead, 2001).

The field of epilepsy research using MEG then moved from simply identifying the irritative zone (region of the brain which generates interictal epileptogenic discharges), to delineating regions of eloquent cortex. The term eloquent cortex is used to define cortical locations that if removed or damaged would result in a loss of sensory processing, linguistic ability or the ability to make controlled movements. Many cases of epilepsy are concurrent with some form of structural deficit, such as a tumour, an infarction or focal cortical dysplasia. It is these types of cases that are particularly suitable for surgical re-section if the structural deficit is shown by some other technique (typically EEG) to also form the epileptogenic zone. These regions are often in or very close to language areas and the sensorimotor cortex. MEG thus became a tool for not only lateralising and localising epileptogenic cortex by measuring spontaneous magnetic fields when the patient was at rest, but also for measuring fields generated during a task in order to allow the localisation of specific perceptual functions.

Primary sensory regions (for example, motor, somatosensory, auditory, visual) can be localised in MEG with relative ease. The tasks are typically simple, the protocols are short and the analyses often a straight-forward extension of the dipolar techniques used to localise spontaneous spike activity. Hund et al. (1997) introduced a measure of surgical risk for cortical lesions located adjacent to the motor cortex. They use the minimal distance between the lesion and sensory and motor cortex as defined by MEG to calculate a functional risk profile. Of the forty patients in the study, 11 patients with gliomas showed a high risk profile and 6 of these individuals underwent non-operative treatment. Of the 28 patients with a low functional risk profile, none showed any neurological deficit postoperatively. Ganslandt et al. (1999) investigated 50 patients who had a tumour resected from around the motor cortex. The sensorimotor cortex was defined in all patients using MEG in conjunction with dipolar modelling techniques. The central sulcus was identified intra-operatively and this localisation was compared with the MEG results with the two showing excellent concordance. The efficacy of localising sensorimotor cortex via MEG has also been compared to electrocorticography recordings. Roberts et al. (2000) compared the mapping of somatosensory motor cortex with intra-operative cortical stimulation and found that the results were concordant in 90% of cases, with a high level of concordance in 77% of cases. One of the reasons for the success of MEG in being able to accurately identify the location of primary sensory areas such as primary auditory, somatosensory, motor and visual cortex is the fact that these are well defined cortical regions. From electrophysiological studies, the cytoarchitecture of these areas in the normal population is known. Not only is the location of these primary cortices well established, but

they represent relatively discrete processing modules. The other function most commonly localised pre-surgically to reduce the risk of removing eloquent cortex is language processing. However, the language network does not have a primary cortex of representation and is more accurately described as a distributed neuronal network.

Simos et al. (1998) introduced a method via which language laterality could be determined in MEG. Individuals were placed in the scanner and the tasks used were a word-matching and a tone matching task. In each task, the portion of the response that was analysed was after the onset evoked from primary sensory cortices which typically occurs between 80 and 150 ms. The latter portion of the response was analysed and ECDs were used to compute an interhemispheric laterality index. A greater number of dipole solutions were found in the left hemisphere in 87% of subjects in response to the word-matching task. This study demonstrated that it was feasible to place an individual in the MEG scanner whilst performing a language task and the event-related fields produced during this task could be modelled using the now well established dipole techniques, and that the results could reveal information regarding the underlying hemispheric dominance. This protocol was then developed and optimised and the next step was to compare the ability of MEG to determine language function with an independent, established technique.

The Intra-carotid Amobarbital Procedure (IAP) (Wada & Rasmussen, 2007) has been a standard pre-operative diagnostic tool in epilepsy patients since its inception in the 1960's. The test involves injection of a barbiturate into one cerebral hemisphere in order to anesthetise it. A language and memory task is then conducted in order to determine the language capabilities of the non-injected hemisphere. The process is then repeated with the other hemisphere injected. The scores from each of the two tests are then used to determine if either cerebral hemisphere shows dominance for language or memory or if the result is a bilateral representation of function. The results of the test are often used to confirm whether or not a patient is suitable for surgical re-section. The procedure is sensitive to differences in vasculature, has strict time constraints which limit the amount of testing possible and is also associated with risk of morbidity. It is therefore desirable to replace this procedure with a non-invasive alternative which is able to provide the same information regarding hemispheric dominance for language function.

Breier et al. (1999) extended the initial implementation of the language lateralisation paradigm in MEG described by Simos et al. (1998) and investigated concordance levels between the IAP and MEG lateralisation metrics in 26 patients suffering from intractable epilepsy. The results confirmed that there were high levels of agreement between the two metrics. This template of performing non-invasive MEG tests of language dominance in parallel with IAP tests (which patients were having regardless) in order to reach a conclusion regarding their suitability for surgical re-section became widely used in order to provide mounting evidence for the ability of MEG to be used as a pre-operative diagnostic tool. Papanicolaou et al. (2004) measured signals in MEG from 100 epilepsy surgery candidates ranging from 8-56 years of age in response to a word recognition task. Single ECDs were used to model the activity and compute a laterality index. The MEG and IAP lateralisations were concordant to a level of 87%. This study was replicated by Doss et al. (2009) using a cohort of 35 surgery candidates. The MEG and IAP laterality results were concordant in 86% of cases, with high levels of sensitivity (80%) and specificity (100%). Breier et al. (2001) performed a similar comparison of MEG and IAP measures of language laterality in children, demonstrating excellent levels of concordance in 17 out of 19 patients. Studies such as these were essential in determining objective criteria with which to improve data quality and the robustness of analysis techniques

in order to allow MEG to be used for mapping language functions in a clinically relevant manner.

2.2 Summary

Since its inception, Magnetoencephalography has been used to investigate the underlying cortical activity related to epilepsy. This began by using MEG as a basic extension of EEG and simply identifying atypical, epileptiform traces of activity. However, with the introduction of the equivalent current dipole, the field rapidly moved to performing source modelling in order to localise the irritative zone. Before MEG was able to be used clinically it required validation by comparing the results to standard, existing methods. The MEG results were rigorously compared to those from EEG and intra-operative recordings. As the field of MEG as a whole began to use the technique to look at the response of specific perceptual and cognitive systems, the field of epilepsy research continued to develop. Pre-surgical mapping was performed on primary sensory areas and to derive estimates of language laterality. Again, at each stage the results from MEG were compared with established techniques such as electrocorticography recordings and the intra-carotid Amobarbital procedure.

As stated previously, there have been many excellent reviews on the role of MEG in the localisation of both irritative zones and regions of eloquent cortex (Frye et al., 2009; Simos et al., 2000). The purpose of the the brief review presented in this chapter is to use the application of MEG to the diagnosis and treatment of epilepsy as a template with which to evaluate progress in other clinically relevant areas. The clinical needs prior to surgical re-section are clearly defined in epilepsy; it is necessary to define the irritative onset zone and if a cerebral lesion is associated with the seizures, to what extent does this area interact with regions of eloquent cortex. MEG measurements combined with dipole modelling are sufficient to be able to provide an answer to these questions in order to allow progression toward rendering a patient seizure free. However, despite the tools existing to allow MEG to be used in the pre-surgical evaluation of these patients, the development of new methods and techniques did not cease. The next section considers more recent advances in signal processing techniques that have been used to further enhance the ability of MEG to non-invasively inform the treatment and management of epilepsy. What becomes clear is that the study of epilepsy via MEG has continued to grow and develop at a similar pace to the development of new technologies and methods within the broader field. Due to this fact, the speed at which the scans can be performed has increased as knowledge about the most effective protocols grows. As confidence in the diagnostic abilities of the technique grows, more and more clinicians become aware of its utility, resulting in MEG being performed routinely at various epilepsy centres around the world, not as an an innovative and exploratory technique but as a valued and essential step in determining the most appropriate intervention (Ray & Bowyer, 2010; Schwartz et al., 2008). If other conditions are to use MEG as part of a routine diagnostic procedure, then it is necessary not only to apply standard analysis techniques, but to use studies of these conditions to drive forward novel and innovative statistical and modelling techniques.

2.3 Recent epilepsy research

The field of MEG research has continued to grow over the past decade, with new methods, analyses and statistical approaches being developed and rapidly applied to the investigation of a vast array of sensory and cognitive systems. The clinically relevant applications of MEG in epilepsy research were initially developed using the ECD, and this analysis method for the localisation of the irritative zone and of eloquent cortex has been shown to be

effective. However, when new techniques were developed, rather than the epilepsy research persisting with what was already shown to work, researchers embraced these new approaches and worked to obtain more robust, more accurate localisations of function and a better understanding of the underlying pathology associated with the illness.

The ECD approach has a number of weaknesses in that it assumes the activity being modelled is a point-like source of activity. It is also a full inverse solution in that each sensor contributes equally to the fit. For example, a current source emanating from the frontal lobe will be best represented on the sensors in the anterior portion of the sensor array. However, the fields measured on the posterior sensors still contribute to the final fit, and it is possible that excluding this information from the model would result in a more accurate inverse estimate. As the activity is treated as a point-like source, there is no estimate of the extent of activation, or in the case of epilepsy data, the extent of the irritative zone or of eloquent cortex. The two other commonly used inverse methods are Minimum Norm Estimation (MNE) (Hämäläinen et al., 1993) and Beamforming (Van Veen et al., 1997). MNE is a distributed source model which estimates the current density at many thousand locations. The locations are fixed to the cortical surface and the orientation of the signals are fixed to be tangential to this surface. The amplitude of these thousands of sources are then estimated from the data. However, MNE can only be applied in a stable manner to averaged data and, as stated, is restricted to the cortical surface. Beamforming is an adaptive spatial filtering technique which assesses the contribution of each voxel within the brain volume to the measured field. Spatial filtering approaches are now common in research that measures signals via MEG and it is a process which can be highly flexible. Beamformer solutions are able to perform whole-head analyses and can also be used to reconstruct the estimated neural time course at any point within the head. These so-called Virtual Electrodes (VE) have the potential to estimate the electrical activity of a source at a specific location with the temporal resolution of the original signal.

These more advanced modelling techniques have been used on data from epilepsy patients and they are potentially able to provide a more satisfactory description of the underlying pathology than ECD techniques alone. Bowyer et al. (2005) used a current density modelling approach termed MR-FOCUSS (Bowyer et al., 2005) to estimate cortical regions of language activation in 27 patients with localised intractable epilepsy. Verb generation and picture naming tasks were used and a laterality index was calculated for each task and three different latencies. One latency captured all language processing (150-550 ms) while the other two focused on activation of Wernicke's area (230-290 ms) and Broca's area (396-460). In 23 of the 24 patients in which a successful IAP measurement was obtained, the laterality of the activity in the 396-460 ms window was in agreement with the IAP result. Three patients showed either a bilateral or undetermined language representation on the IAP, and in one of these patients the lateralisation obtained by the current density estimate was in agreement with intra-cranial measurements. The results of this study suggest that MNE is able to provide information regarding the lateralisation of function in a cohort of patients. Give that the technique estimates neuronal activity at many thousands of cortical locations, and that laterality is calculated over a number of these estimates, it perhaps allows a more stable estimate of laterality than using the number of single location, point-like sources from dipolar models.

Spatial filtering approaches have also been shown to be effective in the localisation of eloquent cortical function. Beamformers typically focus on the total power of a response (Hymers et al., 2010), however in recent years there has been an increase in the number of variations of specific filter implementations. Cheyne et al. (2006) introduced a novel, event-related beamformer (ERB) based on an implementation initially described by Robinson

(2004). Cheyne et al. (2007) investigated the ability of an event-related beamformer to localise somatosensory and auditory cortices in participants with metallic dental implants and controls. The ECD model and ERB technique produced comparable localisations in control participants, but in patients with metallic implants the ECD method was unable to localise the activity whereas the ERB produced results consistent with expected anatomical regions of activation. The event-related beamformer has been shown to reliably localise the motor cortex in paediatric epilepsy patients (Gaetz et al., 2009) and has also been validated against direct cortical stimulations and the results confirm that it is a viable and robust framework with which to perform non-invasive preoperatve investigations (Pang et al., 2008). Robinson et al. (2004) further refined the spatial filtering approach to bias it toward scanning the head for detection of epileptogenic activity. The electrical time series of activation is estimated at many thousands of points within the volume and at each location the excess kurtosis is calculated to give a metric of the "spikiness" of the data. The advantage of these higher level analyses is that they are more robust to low signal-to-noise ratios and provide a better estimate of the spatial extent of these regions. The ECD models the activity as a single point-like source, whereas MNE and beamformer estimates give a greater indication of the extent of activation. These techniques are also more suited to inferential statistical thresholding than the ECD. The MNE and, in particular, beamformer analyses are tools which can be implemented in a number of different ways in order to optimise the analysis to focus on the specific response of interest. When investigating complex and dynamic processes such as language processing and higher cognitive mechanisms, these are highly desirable facets of an analysis. It is likely that the application of MEG to clinical populations other than epileptics will be dependent on the power and flexibility of these techniques being fully exploited.

The MEG community now also benefits from time and the fact that it is no longer a new technique with a relatively small amount of expertise and knowledge within the field. In recent years there has been a rapid increase in the amount of theoretical and methodological work in order to really push the boundaries of what types of analyses are possible with MEG data. The purpose of this section is to outline how these recent advances have already been applied to the study of epilepsy and how the proliferation of novel and specific analysis techniques means the potential of MEG to be used in a wide range of clinical setting becomes very real.

Previously, one logistical downside of MEG was the amount of data acquired, with modern scanners having in excess of 200 sensors and a default sampling frequency of around 600 Hz, the amount of data collected in a single study can be vast. However, with modern computing power now more affordable and more efficient, there are many fewer constraints on the type of analyses it is possible to perform. The fact that data storage and transfer is now much easier to implement and manage allows even more data to be collected. It is therefore now possible to collect data at much higher sampling frequencies and these large datasets can still be manipulated with ease. One area in which there is unexplored potential is in the acquisition of MEG signals in the upper parts of the frequency spectrum. Typically MEG signals are acquired at 300-600 Hz, and for many studies which investigate human neural processes the analyses focus on biological signals below 100 Hz. Recent work however has shown that there may be reliable diagnostic information represented in high frequency oscillations produced by epileptogenic cortex. The presence of fast oscillations, or ripples, at 100-250 Hz and also fast ripples between 250-500 Hz has been demonstrated in depth electrode recordings made from patients suffering from epilepsy (Bragin et al., 1999; 2002). Urrestarazu et al. (2006) investigated high-frequency activity that occurred during the slow wave immediately after an inter-ictal event and found that in patients suffering from epilepsy there was a decrease

in the energy content at frequencies above 100 Hz. Further work demonstrated that ripples were seen in all epilepsy patients in a group of seven and fast ripples were found in five of these patients (Urrestarazu et al., 2007). Furthermore, there was a higher incidence of ripples measured from inside the irritative zone compared to outside it and this effect was even stronger for the incidence of fast ripples. Therefore the existence of high-frequency oscillations could be used to delineate the irritative zone and epileptogenic zone from other regions of cortex.

High frequency oscillations have been detected in MEG and these signals are potentially a more accurate and robust indication of the extent of the epileptogenic zone. Xiang et al. (2009) collected MEG signals at a sampling frequency of 4 kHz from 30 paediatric epilepsy patients. 86% of patients showed high frequency oscillations and 63% showed more than one high frequency component. The range of frequencies varied across patients with a peak of 910 Hz. Localisation of this high-frequency activity was performed with a beamformer and the sites of activation identified were concordant with cerebral lesions in 70% of cases. Eleven of these patients went on to have surgery and the MEG localisations were concordant with intra-operative recordings in 82% of patients. The combination of high frequency data with a spatial filtering approach is therefore potentially more reliable than standard dipolar techniques in the pre-surgical evaluation of epilepsy patients (Xiang et al., 2010). Although there is still much validation work to be done, for example it may be desirable to combine high frequency data with the excess kurtosis beamformer, it is clear that the clinical efficacy of MEG regarding the treatment of epilepsy continues to develop and evolve.

3. Parkinsonism research

Parkinson's disease is a degenerative disorder of the central nervous system with symptoms typically including tremor, rigidity, slowness of movement and postural instability. The current pathophysiological concept of Parkinsonism is that due to a loss of dopaminergic connections from the substantia nigra to the striatum there is abnormal functionality in the basal ganglia (Obeso et al., 2000). This hyperactivity in the subthalamic nucleus leads to inhibition of the thalamus and subsequently the sensorimotor cortex which leads to a loss of bodily movement, known clinically as hypokinesia. This altered connectivity affects the entire motor network, and evidence for the concept was found when high frequency stimulation of the subthalamic nucleus caused a reduction in Parkinsonian symptoms (Krack et al., 1998). As Parkinson's disease is the manifestation of altered connectivity, which causes a change in oscillatory dynamics in cortical areas, it is potentially well-suited to study and detection via MEG. This section aims to outline the advances made, and analyses used in the application of MEG to the identification of this disease. Specific studies are highlighted to show the progression and development within the field (see for example Berendse & Stam, 2007; Stam, 2010; Timmermann et al., 2007, for a more exhaustive review of the literature).

Volkmann et al. (1996) provide one of the earliest studies using MEG to investigate Parkinsonian tremor. As with much of the early epilepsy research, a single ECD model was used to localise activity. The data analysis was biased to focus on oscillatory activations that were concurrent with the observed Parkinsonian tremor. The dipole models showed activity at the diencephalic level and in pre-motor and sensorimotor cortices accompanied the resting tremor. Since it became clear the MEG could be used to investigate the underlying pathology associated with Parkinson's disease there have been a number of follow-up studies. Although the volume of studies is far fewer for Parkinson's disease than for epilepsy, a similar pattern can be seen in the types of studies performed and the progression in complexity of analysis approaches. As was described earlier in the context of epilepsy diagnosis, more

recent investigations of Parkinson's disease using MEG have utilised more specific analysis techniques which are more suitable to studying the disease than the simple ECD.

Many of the analysis methods used focus on characterising the oscillatory dynamics associated with Parkinson's disease at the level of the sensors rather than performing source modelling. Kotini et al. (2005) measured spontaneous MEG signals from 9 Parkinsonian patients with minimal tremor. Each recording was 2 minutes in duration and the eyes remained closed in order to reduce artefacts and increase the alpha rhythm. The power spectrum for each each sensor was calculated by means of a Fast Fourier Transform (FFT) and the first dominant frequency was extracted. In a comparison of controls versus patients, the patients showed a prominent frequency which was lower than the 6 Hz typically observed in the healthy controls. The spatial distribution of power in these patients tended to be over a wide region in the low-frequencies whilst healthy controls showed a more focal topography for their higher frequency predominant activity. Bosboom et al. (2006) used similar techniques to investigate oscillatory differences between demented and non-demented Parkinsonian patients. Spontaneous neuronal signals were measured via MEG from 13 demented and 13 non-demented patients whilst off medication. Two 13-second epochs were used for data analysis and the data filtered in to delta, theta, alpha, beta and gamma bands of activity. The MEG sensors were also grouped into regions of interest i.e. frontal, central, parietal and occipital on both side of the sensor array. Non-demented patients showed a diffuse increase in theta power and a decrease in beta power relative to controls in central and parietal channels. Demented Parkinson's disease sufferers showed a diffuse increase in delta and theta power and a simultaneous decrease in relative alpha and beta bands when compared to the non-demented controls. Stoffers et al. (2007) used the same technique to show that the slowing of oscillatory dynamics is a feature of non-demented Parkinson's patients from a very early stage in the disease and this is independent of disease duration, severity and dopaminergic treatment. Stoffers et al. (2008) also investigated differences between patients in the early and later stages of the disease. In this study, the same frequency bands and sensor topography was used but instead of calculating changes in total power, or changes in relative power between two populations of patients, synchronisation likelihood (SL) was calculated. SL is used to to estimate both linear and non-linear correlations between time-series. SL was calculated both within and between specific topographic regions within the sensor array. The results showed that early-onset, drug naive patients showed an increase in SL in the 8-10 Hz band relative to controls whilst disease duration was positively related to 10-13 and 13-30 Hz. The 8-10 Hz was therefore thought to represent increased resting-state cortico-cortical connectivity from the onset of the disease and this altered connectivity extends to neighbouring frequency regions as the disease progresses.

It is highly encouraging that differences between patients suffering from Parkinson's disease and healthy controls can be observed at the level of the sensors. Furthermore, differences between demented and non-demented, early and late onset sufferers can also be detected. These studies suggest that the underlying pathology of the disease may have specific representations in certain frequency bands and in specific parts of the sensor array. The clinical utility of these observations is that MEG could be used to obtain an objective measure of the specific nature of Parkinson's disease and also when diagnosed, the technique may be used to provide an estimate as to the duration of the disease and to provide a measure of the rate of decline. Although it is encouraging that differences can be seen at the sensor level in a population of Parkinsonian patients, the analyses in some cases are highly rudimentary. It may be that specific types of Parkinson's disease can be identified via the oscillatory activity measured at the MEG sensors without any inverse modelling, and that this framework can

be extended to other neurodegenerative disease. It is not the case that the more complex and mathematically intricate an analysis is the more accurate or robust it becomes, and therefore constraining analyses to the sensor domain may be entirely appropriate in some cases and extremely effective. However the method of peak-picking in the spectral domain is highly simplistic as well as being statistically weak. For example it is unclear if this type of activity is associated with other illnesses, or how prevalent such activity is the normal population. The use of synchronisation likelihood is a more powerful technique, but it is still limited to the analysis of data on the sensors. Parkinson's disease is thought to manifest as the altered connectivity between cortico-cortical connections and thus what the MEG is able to measure is how these changes in connectivity affect the global brain dynamics. There are a number of problems associated with performing connectivity analyses at the level of the sensors, and these issues all essentially stem from the issue of field spread. Due to the fact that a neuronal source is measured by a number of sensors it is possible to observe long-range interdependencies between MEG sensors and any change seen in the specific connectivity measure chosen could be due to a number of reasons (Schoffelen & Gross, 2009). Therefore, although the initial results are promising in that differences between clinical populations can be observed, the techniques and analyses require more robust validation. One method for mitigating the effect of field spread to some degree is to perform the analyses in source space rather than sensor space. As discussed earlier, the spatial filtering framework is a flexible approach which can be tailored to focus on specific responses, and even with the relatively small number of studies on Parkinson's disease patients, at least compared to epilepsy studies, already the field has start driving forward innovative and specific analysis approaches.

Gross et al. (2001) introduced a specific beamformer implementation to focus on cortico-cortical connectivity. The Dynamic Imaging of Coherent Sources (DICS) approach is a frequency-domain spatial filter implementation that allows coherence to be estimated throughout the brain volume. Each location within the brain is compared to a reference measure of coherence, which can be taken from an external source such as an electromyogram (EMG) or from a specific region of interest within the brain volume. In a single patient suffering from idiopathic Parkinson's disease, spontaneous activity was recorded for 5 minutes in conjunction with an EMG. Cortico-muscular coherence was estimated in the 9-12 Hz frequency band as this range contained the largest component in the power spectrum of the EMG. The resultant volumetric image showed peak levels of coherence in the contralateral primary motor cortex. This approach was shown to be more robust than using signals recorded on the sensors. Timmermann et al. (2003) extended this case study example to a cohort of 6 individuals suffering from tremor-dominant Parkinson's disease in order to better characterise the oscillatory network involved in Parkinson's disease. When off medication patients showed a dominant 4-6 Hz tremor which cohered strongly with the EMG. The main frequency of cerebro-cerebral coherence was at double this tremor frequency. Thalamic and cerebellum activity showed a broad peak of coherence around 20 Hz. They reported a bi-directional coupling between the EMG and cortical areas such as the posterior parietal cortex and secondary somatosensory cortex.

Litvak et al. (2010) used a spatial filter analysis to analyse MEG recordings from patients with electrodes inserted into the subthalamic nucleus to allow deep brain stimulation of the structure. Such a procedure can be used to treat Parkinson's disease by electrically stimulating the subcortical structure in an attempt to realign the oscillatory dynamics of the cortico-cortical loop. In many ways this is analogous to the comparison of electrocorticography recordings in epilepsy patients and ascertaining to what extent the MEG can be an accurate and reliable measure of the underlying neuronal activity. The inserted

electrode not only has the ability to deliver a current to the area, but to also record signals. MEG data were acquired from a single Parkinsonian patient and a healthy control whilst at rest and also whilst performing a simple, and then a more complex motor task. An electro-oculargram and EMG were acquired simultaneously. The inherent noise-cancelling effect of a beamformer was used to localise source activity despite the large signals produced by the implanted electrodes and associated hardware. The DICS beamformer was used to localise cortical sources that were coherent with signals in the subthalamic nucleus detected by the inserted electrode, to estimate the time course of cortical activity using a virtual electrode and to uncover volumetric regions associated with movement-related power changes. Litvak et al. (2011) extended this use of the DICS beamformer into a larger cohort of 13 Parkinson's disease patients with a view to describing the dynamics of the cortico-subthalamic loop rather than focusing on methodology. Two different networks were identified which were distinct both in spectral power and spatial location. A temporoparietal-brainstem network was coherent with recordings from the subthalamic nucleus in the 7-13 Hz frequency range, whilst a frontal network was coherent with subthalamic recordings in the 15-35 Hz range. It was also noted that dopamine levels increased the coherence of this frontal network. It is possible that these networks represent distinct manifestations of the disease and if they can be better characterised may lead to a more successful diagnosis of the different Parkinsonian subtypes to ensure that patients receive the correct treatment at the earliest possible stage in the disease onset.

The other potential clinical utility of MEG in the diagnosis and treatment of Parkinson's disease is to quantify the affects that external cortical stimulation has on a patients symptoms. Mally & Stone (1999) describe a study in which the application of transcranial magnetic stimulation (TMS) was shown to alleviate Parkinsonian symptoms in a group of 10 patients. TMS is a technique whereby a focused, high-amplitude magnetic field is produced by a coil positioned outside the head which induces electrical activity within the brain. The therapeutic effects of TMS and direct current stimulation (a technique which also induces electrical activity within the brain) have been demonstrated to be long-lasting (Lefaucheur et al., 2004; Wu et al., 2008). However, it can clearly be seen in a systematic review of the literature by Fregni et al. (2005) that the mechanisms by which symptoms are alleviated as well as the optimal parameters of stimulation duration, frequency etc are unknown. MEG has been used to try and uncover the reasons why techniques such as TMS are able to alleviate symptoms. If this can be uncovered then it would greatly enhance the efficacy of this intervention and also allow it to become more commonly used. Anninos et al. (2007) recorded one minute of MEG data from 30 patients diagnosed with idiopathic Parkinson's disease both before and after the application of TMS. Patients were divided into two group of partial responders and favourable responders. Partial responders were patients whose tremor or dyskinesia returned within 12 months and showed a low-amplitude alpha rhythm in their subsequent EEG. Favourable responders showed no Parkinsonian symptoms for a year and showed a high-amplitude alpha rhythm. The only MEG analysis performed in this study was to label the pre and post stimulation recording as one of normal, abnormal or partially normal. Therefore the analysis allows no insight into how the intervention alters the cortico-cortical network in order to alleviate symptoms. A more systematic study could use MEG to quantify the oscillatory dynamics of the network before and after TMS is applied with a number of different sub-groups, each one receiving a different set of parameters. In such a study MEG may be able to provide a clear insight as to why the TMS has such a profound benefit, and then efforts can be focused on optimising the magnitude and duration of any alleviation from symptoms.

3.1 Summary

Numerous studies have provided evidence for the fact that MEG is able to measure oscillatory dynamics related to Parkinson's disease at the levels of the sensors. Differences have been seen not only between recordings from patients and healthy controls but also between different phenotypes of the disease. Further validatory studies are needed to build on the evidence for the ability of MEG to to accurately observe the effects of altered connectivity between subcortical and cortical structures. However, the initial work is promising and suggests that the technique may well have a role to play in improving diagnosis of the disease, monitoring specific interventions and evaluation of the effect of specific pharmacological treatments. MEG can potentially provide an objective means by which to determine the specific type of Parkinson's disease, which may lead to the most effective treatment being administered quickly. The technique may also be able to be of predictive value in determining the likelihood of severe and rapid dementia being co-morbid with the disease. The progression of analysis techniques in many ways matches that of epilepsy research, with initial studies using the ECD before more specific analysis tools were adopted that are more appropriate to the response of interest, such as a spatial filter that is sensitive to coherence. Spontaneous recordings are often made, but movement tasks are also used as it is known that the motor network is involved in the disease. As the range of statistical analyses grow and are developed with the specific goal of characterising cortico-cortical loops, the clinical application of MEG to populations of Parkinsonian patients in a routine and systematic way is likely to move from possessing great potential to a real possibility.

4. Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disease and detecting individuals who are susceptible to the condition and achieving an accurate and early diagnosis is an essential step in developing and quantifying effective therapies. As with previous sections, the aim is to not to provide an exhaustive review of the literature to date (for such a review see Criado et al., 2006), but to give an overview of the progress made in the uses of MEG to investigate Alzheimer's disease. Berendse et al. (2000) provided an initial description of the oscillatory changes involved in Alzheimer's disease by measuring the resting-state MEG from a group of 5 patients and 5 age-matched controls. Power and coherence were calculated in a number of frequency bands and the patients showed a greater magnitude and diffusion of low-frequency signals, predominantly in the frontal regions. Higher frequency power was decreased in patients over temporal and occipital regions. In patients, the coherence values at all frequencies were found to be lower than in controls. which suggests that there may be readily available metrics with which to quantify the extent of the condition. Fernández et al. (2006) extended this into a more thorough analysis of the spectral content of MEG data acquired from Alzheimer's patients and reported that oscillatory activity in the 2-4 Hz and 16-28 Hz ranges showed high degrees of sensitivity and specificity when classifying data as from a patient or a control. When measuring signals from patients suffering from Alzheimer's disease, it is common to not only acquire resting-state oscillatory changes, but also those involved in a task. For example Pekkonen et al. (1996) noted that in patients, the auditory response to simple tones was delayed when compared to age-matched controls. The P50 and N100 are standard responses that occur originate from primary auditory cortices in response to tones with simple pitch and amplitude characteristics. The study demonstrated that if the sound was played to a single ear, these early sensory responses were delayed in the ipsilateral but not contralateral hemisphere of patients. Pekkonen et al. (2001) extend this finding to look at the process of performing auditory discriminations, i.e. a task with some

decision process and active listening rather than looking at passive, automated responses. The results confirmed that ipsilateral auditory areas showed a delayed response, although this did not affect the patients' ability to perform the auditory discrimination task. These findings suggest that it may be possible to use abnormal processing in sensory systems to perform an objective assessment of Alzheimer's disease and that these changes need not necessarily be associated with impaired cognitive or sensory percepts. Of course the difficulty is then to determine whether delayed auditory processing points to the onset of Alzheimer's disease or the onset of some other condition.

Another task which is used to investigate cortical dynamics in Alzheimer's disease is a memory task, which is concordant with one of the prominent features of the disease being impaired memory. Maestú et al. (2001) used a high load probe task in which targets needed to be remembered and distinguished from distractors. Control subjects were reported to show an increased number of sources over temporal and parietal regions 400-700 ms after the stimulus onset, whereas Alzheimer's patients showed a greater number of sources over frontal motor areas. The number of sources in patients' left parietal regions was also predictive of their performance on clinical scales of cognitive functioning. In a second study, these left parietal sources were also found to be correlated with the level of hippocampal atrophy (Maestú et al., 2003). One of the potential clinical applications of MEG in the diagnosis and treatment of Alzheimer's disease is to be able to predict which individuals are susceptible to the disease and how rapid their decline may be. Alzheimer's disease has a long pre-clinical stage and Mild Cognitive Impairment (MCI) is often used to describe individuals who are declining from normal cognitive function to dementia. There is a conversion rate of MCI to Alzheimer's disease of around 10-15% per year (see Shah et al., 2000, for a review). Fernández et al. (2006) assessed the ability of MEG to determine the risk factor associated with individuals with MCI developing Alzheimer's disease. Dipoles were fitted to the low-frequency regions of the spectrum of resting-state recordings. Dipole density in the left parietal regions fitted over the delta frequency band were found to provide a reliable classification of Alzheimer's and MCI patients. MCI patients were also categorised as being at either low or high risk based on the observed magnetic fields. A follow-up clinical examination occurred 2 years later and the fact that more patients in the high MCI group had developed Alzheimer's disease than the low MCI group suggests that MEG can be a useful clinical utility for identifying risk factors for individuals. Osipova et al. (2006) conducted a study with a similar goal of predicting transition from MCI to Alzheimer's disease, and reported that the source distribution of the alpha rhythm was abnormal in Alzheimer's patients but not MCI patients when compared to controls, and so the changes in neuronal processes associated with MCI may be more subtle and more complex than those associated with other neurodegenerative diseases. Of course more longitudinal studies are required and, like other techniques discussed in this chapter, it may be desirable to move away from a simple dipolar technique and investigate the dynamics using other methods, but the initial results are promising.

Spatial filtering approaches have also been applied to Alzheimer's disease data which, as previously discussed, offers a more complete description of the data as it treats the activity as a distributed network rather than point-like bursts of activity. Alzheimer's, MCI and control patients were scanned and the two patient groups were noted not to show any slow-wave MEG activity in conjunction with the task, which was simply closing the eyes and opening them at 10 second intervals. The beamformer analyses revealed all three groups had increased activity in posterior regions when the eyes were closed in the 8-15 Hz band. Patients suffering from Alzheimer's disease showed greater activity in frontal regions in this frequency band when the eyes were closed compared to controls, whereas MCI patients showed no such

difference. This finding was taken to show that alpha activity is found in frontal regions for Alzheimer's patients across a cohort, whereas the same is not true for MCI patients or controls. These findings, both in the spectral frequencies involved and the volumetric locations are consistent with previous results. Further analyses also confirmed that these changes in activity were correlated with clinical examinations of the mental state of the Alzheimer's disease patients (Ishii et al., 2010).

Dipolar and beamformer approaches have been shown to provide an objective measure which can categorise an individual as suffering from Alzheimer's disease. Such a technique could be valuable in the treatment of a disease that is difficult to diagnose and categorise. However, as the disease affects cognitive function in a general way, and in a manner that is only broadly consistent across individuals, applying these analyses to resting-state data may not be the best use of the technique. A number of higher-level techniques have been applied to MEG data acquired from Alzheimer's disease patients. Poza et al. (2008) used techniques from information theory to discriminate the resting-state data from a group of individuals and age-matched controls. Power spectral densities were calculated from the data and three different methods were used to compute the spectral entropy of the signals. Entropy can be thought of as a measure of uncertainty and it was demonstrated that Alzheimer's patients showed significantly lower levels of entropy than control participants. On the basis of these entropy measures, data from individuals were accurately identified as from patient or controls to a level of 87% and suggest a loss of irregularity in the dynamics of Alzheimer's patients. A similar finding, that data from Alzheimer's patients is more regular than that from controls, was reported using approximate entropy (Gomez et al., 2010). It is therefore possible that higher level statistical analyses may be more robust to detecting the signature oscillatory characteristics of Alzheimer's disease. It is these types of innovative, robust approaches that, when developed with specific clinically relevant questions in mind can allow MEG to be applied reliably to groups of patients suffering from illness and disease. Although much more is needed, both in terms of basic research and clinical trials in the efficacy of MEG in the identification and monitoring of neurodegenerative disease, the clinical applications are clear and the benefits are potentially vast.

5. Future applications

Specific diseases have a well defined biomagnetic representation. For example epileptogenic activity is typically high amplitude and can be characterised as slow wave activity or "spike-and-wave" activity. It has a strong dipolar representation on the sensors and is therefore readily identified both visually and statistically. Other types of illness such as Parkinson's disease show more complex temporal dynamics in the measured MEG, however there are still typical spectral shapes which can be used to identify the illness, for example diffuse and exaggerated low-frequency information. Parkinson's disease is also known to affect connectivity related to motor cortices and so there is a priori information regarding sensors and cortical regions of interest. There are however, numerous diseases which do not have such clearly defined neuromagnetic representations. However, some of these illnesses are still suitable to diagnosis and detection via MEG. Detection of certain illnesses is possible via a neural system largely unrelated to the symptomatic manifestation of the disease. "Biomarker" is a term often used to describe the observation of altered or atypical processing in one domain which provides an independent measure of another function, in this case an objective measure related to an illness or disease. Such a measure may allow early and effective diagnosis, to evaluate different interventions or to predict an individuals responsiveness to a drug or their rate of decline. This final section gives a brief overview

of some of the recent applications of MEG in the identification of biomkarkers for specific conditions.

The application of MEG measurements to patient populations is clearly still developing and evolving. One of the biggest risk factors in developing neurodegenerative disorders is age and although, as previously discussed, MEG is able to provide a measure of the underlying neuronal activity associated with these diseases, the changes in oscillatory dynamics in the normal aging population are still poorly understood. Rossini et al. (2007) note that MEG can be used in conjunction with other imaging modalities in order to distinguish between physiological and pathological aging. In order to more robustly identify neurodegenerative disease it is essential that the aging brain is more fully characterised. This needs to be done not purely in terms of the dominant spectral frequencies of the data, but also using higher-level metrics such as coherence, entropy etc. The statistical robustness of diagnosing diseases such as Parkinson's and Alzheimer's will then increase as the distribution of the normal population can be characterised and these conditions may be more clearly identified.

MEG has been used to investigate responses associated with schizophrenia and schizoaffective disorder. Uhlhaas et al. (2008) provide a review of the role of oscillatory rhythms in cortical networks in relation to the illness. The role of delta, theta, alpha, beta and gamma rhythms are often discussed in relation to a range of neural processes such as memory, language, auditory and visual processing. The synchrony and amplitude of these rhythms during a range of behavioural tests are seen to be altered in patients suffering from Schizophrenia, and so investigation of these processes via MEG may provide an insight into the development and manifestation of the disease. More specific examples include altered auditory processing in response to deviant sounds. The Mismatch Negativity (MMN) paradigm is often used to investigate automatic auditory processing. A sequence of identical stimuli are played and a deviant stimulus is inserted at random. For example, in the middle of a train of 500 Hz tones, a 550 Hz tone is heard. The response to this deviant is amplified and an insight into the auditory system can be obtained. Näätänen & Kähkönen (2009) describe data which demonstrates that in schizophrenic individuals the MMN is attenuated. The MMN in response to frequency deviation is also found to be attenuated in a manner that reflects the progress of the disease as measured by disease duration. There is also evidence that specific characteristics of the MEG measured in response to auditory stimulation may implicate the patients possessing positive or negative symptoms. Reite et al. (2010) retrospectively investigated differences between the auditory steady-state response of patients with schizoaffective disorder and schizophrenia and suggest that whereas the amplitude and phase of the response is atypical in schizophrenia sufferers, the schizoaffective disorder patients are more similar to controls. Differentiating between schizophrenia and schizoaffective disorder is a difficult and unclear process, however differential diagnoses lead to different interventions and different paths of pharmacological treatment. Therefore the potential ability of MEG to differentiate between the two could have great clinical utility. Ince et al. (2008) used a working memory task and demonstrated differences between schizophrenic patients and controls in specific parts of the sensor array and in specific frequency bands.

Autism spectrum disorder (ASD) is another condition that has received interest from researchers who use MEG as a measure of neuronal functioning. ASD encompasses a number of illnesses including Autism disorder and Asperger's syndrome. The conditions are most commonly diagnosed in childhood and therefore early detection may be able to limit the impact they have on development into adulthood. Again, the auditory system appears to be reliably associated with the underlying nature of the conditions, with ASD patients showing

both delayed and attenuated responses to simple sounds when compared to age-matched controls. Roberts et al. (2010) presented tones of different frequencies to a group of ASD and healthy controls and analysed the M50 and M100 response from both left and right superior temporal gyri. No differences were seen between groups for the amplitude or latency of the M50 but the M100 response was delayed in ASD patients by an average of 11 ms across the entire group. One clear difference between ASD and the other conditions discussed in this chapter is that ASD is a neurodevelopmental disorder, and therefore by its very definition affects the paediatric population. This therefore amplfies some of the inherent challenges of scanning patients in MEG, such as movement of the head and trunk and also stresses the need to design protocols that can be easily understood and tolerated by young individuals. Scanning children in MEG is a time consuming and difficult process, and the data are more susceptible to artefacts. However, given the prevalence of ASD, the potential benefits of using MEG as a screening tool to allow early identification of the illness make the technique a valuable one.

Georgopoulos et al. (2007) made MEG recordings from 142 individuals whilst they fixated on a spot of light for 45-60 seconds. The analysis stream utilised the sensor information and assessed zero-lag cross-correlations in order to provide an estimate of synchronous coupling. The analyses appear to provide some insight regarding which subset of clinical conditions each participant could be categorised as matching. Patients with multiple sclerosis, Alzheimer's disease, schizophrenia, Sjogren's syndrome, alcoholism, and facial pain as well as a group of control participants were reliably identified. A second study by the same group applied similar techniques to a group of patients suffering from post-traumatic stress disorder (Georgopoulos et al., 2010). Although a study which attempts to differentiate so many different conditions is susceptible to limitations in the analysis and a lack of statistical robustness, the results are extremely promising and highlight the powerful nature of MEG as a non-invasive tool with which to objectively evaluate clinical populations.

MEG has also been found to have a clinical utility unrelated to measures of functional mechanisms. Martino et al. (2011) used MEG to look at the functional connectivity of the so called "resting-state network". The resting-state network is used to describe the cortical dynamics that can be observed in the absence of any task. Functionally connected regions still communicate with each other and decreased levels of connectivity in this network are expected in many types of illness and disease. Functional connectivity is an umbrella term used to describe a series of analysis methods which focus on measures of coherence, correlation and synchronisation. A brief overview of some of these metrics has been given in previous sections of this chapter, however it is worth noting that measures of connectivity are becoming more and more sought after by researchers of human brain function. The advantage of studying the resting-state connectivity of areas is that no task is required, which means the recodring can be short and can be carried out in patients who may struggle to perform a language, memory, or movement task. Martino et al. (2011) created functional connectivity maps using imaginary coherence and the aim was to determine if this information could predict the results of intra-operative electrical stimulation (IES) carried out to identify eloquent regions of cortex. 57 patients with tumours in or near motor, sesnory or language areas were studied. A lesion-related area of cortex was identified and compared to a representative number of points taken from the whole of the brain, as a control the lesion-related area was compared to the same area in the contralateral hemisphere. The results revealed MEG functional connectivity maps to have a 100% negative predictive value, which means that when the connectivity in the lesion-related area was lower than the contralateral volume in each of these patients (a total of 7), no functional areas were idenitied

in the lesion via IES. In 42 subjects, at least some voxels in the lesion-related area showed increased connectivity and in 64% of these patients, IES revealed a functionally active area. The authors stress that the study must be repeated on a larger sample of patients but, as they also note, the potential clinical utility of such information has a potentially huge impact upon pre-surgical planning and investigation. These recordings are very short and require no active participation in a task, or any attentional processes. The study presented attempts to use robust statisatical analyses to evaluate the responses, a facet which is missing from MEG studies in a number of areas. The resting-state network, also known as the default-mode network, has become a hot topic in both fMRI and MEG in recent years.

Currently, a large number of metrics are used to obtain an estimate of so-called functional connectivity. Methods such as coherence, imaginary coherence, phase lag index and synchronisation likelihood are currently being applied to MEG recordings from both patients populations and healthy controls. Although they differ in their underlying mathematics, their specific assumptions are the same, that distant brain regions that are communicating with each other will have an observable MEG signal which is very similar. The main problem for all the methods is also the same, that of field spread. This results from the fact that any inverse estimate is calculated using only the sensor data, and this information is the same when estimating activity coming from region *A* and region *B*. Therefore spurious connectivity becomes highly likely given that the same sensor data is used to obtain both inverse estimates. It is likely that in the coming years a number of these methods will emerge as being favoured. This must be because they are 1) the most robust to spurious connectivity and 2) they are suitable for statistical interrogation. If the application and devlopement of these connectivity measures can be done in clinical populations in parallel with healthy controls then the resting-state network, and estimates of the connectivity present within the network, has the potential to be a clinically relevant tool which is not limited to a specific sub-type of illness. Such a measure could be used a a preliminary screening tool for a range of conditions, however if the clinical utility of such an approach is to be maximised, it is essential to fully characterise the network in the normal population and then develop statistically viable ways of identifying how different diseases affect the network.

6. General summary

This chapter has outlined the current clinical utility of MEG by charting the progression of analyses and methodologies in a range of different clinical populations. What is striking is the similarity which exists in the progression of the technique across different sub-types of illness and disease, despite the fact that these advances were made at very different moments in time. Epilepsy is by far still the area which is able to obtain the most clinically relevant information from MEG scans. The initial role of MEG in epilepsy diagnosis and management was to identify atypical waveforms, much in the same way as EEG was used. This was then followed by the use of dipole fitting techniques to estimate the brain location responsible for the epileptogenic activity. Dipolar techniques were then applied to various perceptual and cognitive functions in the epileptic population to delineate eloquent cortex before more advanced modelling techniqes such as minimum-norm estimation and spatial filters were used to better characterise the dynamic changes in neuronal activity. These advances took somewhere in the region of two decades, as the field of epilepsy research via MEG managed to maintain pace with the general field of MEG research. Subsequently, MEG has been used to investigate the underlying dynamics of a range of illness and disease, and although the developments have occurred at a greater pace, the general pattern persists; dipole fits are first applied to passive resting data, they are then applied to more complex perceptual and

cognitive tasks before more complex modelling criteria are used altogether. MEG has been shown to be able to reliably distinguish the length of onset of a disease, to accurately identify an individual as being a patient or a healthy control, and to predict the probability of a patient suffering further decline. The type of illness and disease that these effects have been shown for are typically difficult to detect clinically until relatively late in the progression of the disease. Therefore the early, accurate and reliable diagnosis of these conditions can allow patients to receive the appropriate intervention as soon as possible.

The methodological advances in MEG now occur at a rapid pace, with ever more eloquent and complex measures of coherence and correlation applied to investigate mechanisms of functional connectivity. Many of these measures have been shown, in small samples, to have a potential clinical utility. Due to MEG now being more widely used and better understood than in the early days of epilepsy research the field is in an extremely promising position. Much work is needed over the coming years to validate these initial clinical findings. Independent clinical tests are needed to support the information obtained via non-invasive biomagnetic measurements. Longitudinal studies are required to determine the accuracy and sensitivity with which MEG is able to predict the onset and development of certain conditions. Comprehensive and thorough research studies are needed to determine the most robust algorithms with which to measure coherence between different brain regions, and there needs to be clear bi-directional communication between scientists and clinicians to establish what the clinically relevant questions are and if MEG is technique which is able to add extra information to the diagnosis of a range of conditions. There is no doubt that the evidence for the clinical utility of MEG is compelling, It is no longer a technique reserved for identifying epileptiform activity, it is now a technique with the potential to provide an insight into the underlying neuronal activity of pathologies which currently no other invasive or non-invasive method can. There is much confirmatory work to be done but, MEG clearly does have the potential to become a routinely used method to aid in the diagnosis and treatment plan of a range of diseases which manifest themselves as cerebral deficits.

7. References

Abbott, J. A. & Schwab, R. S. (1948). Some clinical aspects of the normal electroencephalogram in epilepsy., *N Engl J Med* 238(14): 457–461.
URL: *http://dx.doi.org/10.1056/NEJM194804012381401*

Anninos, P., Adamopoulos, A., Kotini, A., Tsagas, N., Tamiolakis, D. & Prassopoulos, P. (2007). Meg evaluation of parkinson's diseased patients after external magnetic stimulation., *Acta Neurol Belg* 107(1): 5–10.

Berendse, H. W. & Stam, C. J. (2007). Stage-dependent patterns of disturbed neural synchrony in parkinson's disease., *Parkinsonism Relat Disord* 13 Suppl 3: S440–S445.
URL: *http://dx.doi.org/10.1016/S1353-8020(08)70046-4*

Berendse, H. W., Verbunt, J. P., Scheltens, P., van Dijk, B. W. & Jonkman, E. J. (2000). Magnetoencephalographic analysis of cortical activity in alzheimer's disease: a pilot study., *Clin Neurophysiol* 111(4): 604–612.

Bosboom, J. L. W., Stoffers, D., Stam, C. J., van Dijk, B. W., Verbunt, J., Berendse, H. W. & Wolters, E. C. (2006). Resting state oscillatory brain dynamics in parkinson's disease: an meg study., *Clin Neurophysiol* 117(11): 2521–2531.
URL: *http://dx.doi.org/10.1016/j.clinph.2006.06.720*

Bowyer, S. M., Fleming, T., Greenwald, M. L., Moran, J. E., Mason, K. M., Weiland, B. J., Smith, B. J., Barkley, G. L. & Tepley, N. (2005). Magnetoencephalographic localization of the

basal temporal language area., *Epilepsy Behav* 6(2): 229–234.
URL: *http://dx.doi.org/10.1016/j.yebeh.2004.12.003*

Bowyer, S. M., Moran, J. E., Weiland, B. J., Mason, K. M., Greenwald, M. L., Smith, B. J., Barkley, G. L. & Tepley, N. (2005). Language laterality determined by meg mapping with mr-focuss., *Epilepsy Behav* 6(2): 235–241.
URL: *http://dx.doi.org/10.1016/j.yebeh.2004.12.002*

Bragin, A., Engel, J., Wilson, C. L., Fried, I. & BuzsÃąki, G. (1999). High-frequency oscillations in human brain., *Hippocampus* 9(2): 137–142.
URL: *http://dx.doi.org/3.0.CO;2-0*

Bragin, A., Mody, I., Wilson, C. L. & Engel, J. (2002). Local generation of fast ripples in epileptic brain., *J Neurosci* 22(5): 2012–2021.

Breier, J. I., Simos, P. G., Wheless, J. W., Constantinou, J. E., Baumgartner, J. E., Venkataraman, V. & Papanicolaou, A. C. (2001). Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: a comparison., *J Child Neurol* 16(2): 124–130.

Breier, J. I., Simos, P. G., Zouridakis, G., Wheless, J. W., Willmore, L. J., Constantinou, J. E., Maggio, W. W. & Papanicolaou, A. C. (1999). Language dominance determined by magnetic source imaging: a comparison with the wada procedure., *Neurology* 53(5): 938–945.

Cheyne, D., Bakhtazad, L. & Gaetz, W. (2006). Spatiotemporal mapping of cortical activity accompanying voluntary movements using an event-related beamforming approach, *Hum Brain Mapp* 27(3): 213–229.

Cheyne, D., Bostan, A. C., Gaetz, W. & Pang, E. W. (2007). Event-related beamforming: a robust method for presurgical functional mapping using meg., *Clin Neurophysiol* 118(8): 1691–1704.
URL: *http://dx.doi.org/10.1016/j.clinph.2007.05.064*

Criado, J. R., Amo, C., Quint, P., Kurelowech, L. & Otis, S. M. (2006). Using magnetoencephalography to study patterns of brain magnetic activity in alzheimer's disease., *Am J Alzheimers Dis Other Demen* 21(6): 416–423.
URL: *http://dx.doi.org/10.1177/1533317506293502*

da Silva, F. H. L. (2005). What is magnetoencephalography and why it is relevant to neurosurgery?, *Adv Tech Stand Neurosurg* 30: 51–67.

Doss, R. C., Zhang, W., Risse, G. L. & Dickens, D. L. (2009). Lateralizing language with magnetic source imaging: validation based on the wada test., *Epilepsia* 50(10): 2242–2248.
URL: *http://dx.doi.org/10.1111/j.1528-1167.2009.02242.x*

Ebersole, J. S. (1997). Magnetoencephalography/magnetic source imaging in the assessment of patients with epilepsy., *Epilepsia* 38 Suppl 4: S1–S5.

Fernández, A., Hornero, R., Mayo, A., Poza, J., Maestü, F. & Ortiz, T. (2006). Quantitative magnetoencephalography of spontaneous brain activity in alzheimer disease: an exhaustive frequency analysis., *Alzheimer Dis Assoc Disord* 20(3): 153–159.

Fernández, A., Turrero, A., Zuluaga, P., Gil, P., Maestü, F., Campo, P. & Ortiz, T. (2006). Magnetoencephalographic parietal delta dipole density in mild cognitive impairment: preliminary results of a method to estimate the risk of developing alzheimer disease., *Arch Neurol* 63(3): 427–430.
URL: *http://dx.doi.org/10.1001/archneur.63.3.427*

Fregni, F., Simon, D. K., Wu, A. & Pascual-Leone, A. (2005). Non-invasive brain stimulation for parkinson's disease: a systematic review and meta-analysis of the literature., *J*

Neurol Neurosurg Psychiatry 76(12): 1614–1623.
URL: *http://dx.doi.org/10.1136/jnnp.2005.069849*

Frye, R. E., Rezaie, R. & Papanicolaou, A. C. (2009). Functional neuroimaging of language using magnetoencephalography., *Phys Life Rev* 6(1): 1–10.
URL: *http://dx.doi.org/10.1016/j.plrev.2008.08.001*

Gaetz, W., Cheyne, D., Rutka, J. T., Drake, J., Benifla, M., Strantzas, S., Widjaja, E., Holowka, S., Tovar-Spinoza, Z., Otsubo, H. & Pang, E. W. (2009). Presurgical localization of primary motor cortex in pediatric patients with brain lesions by the use of spatially filtered magnetoencephalography., *Neurosurgery* 64(3 Suppl): 177–85; discussion 186.
URL: *http://dx.doi.org/10.1227/01.NEU.0000316433.10913.32*

Ganslandt, O., Fahlbusch, R., Nimsky, C., Kober, H., Mller, M., Steinmeier, R., Romstck, J. & Vieth, J. (1999). Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex., *J Neurosurg* 91(1): 73–79.
URL: *http://dx.doi.org/10.3171/jns.1999.91.1.0073*

Georgopoulos, A. P., Karageorgiou, E., Leuthold, A. C., Lewis, S. M., Lynch, J. K., Alonso, A. A., Aslam, Z., Carpenter, A. F., Georgopoulos, A., Hemmy, L. S., Koutlas, I. G., Langheim, F. J. P., McCarten, J. R., McPherson, S. E., Pardo, J. V., Pardo, P. J., Parry, G. J., Rottunda, S. J., Segal, B. M., Sponheim, S. R., Stanwyck, J. J., Stephane, M. & Westermeyer, J. J. (2007). Synchronous neural interactions assessed by magnetoencephalography: a functional biomarker for brain disorders., *J Neural Eng* 4(4): 349–355.
URL: *http://dx.doi.org/10.1088/1741-2560/4/4/001*

Georgopoulos, A. P., Tan, H.-R. M., Lewis, S. M., Leuthold, A. C., Winskowski, A. M., Lynch, J. K. & Engdahl, B. (2010). The synchronous neural interactions test as a functional neuromarker for post-traumatic stress disorder (ptsd): a robust classification method based on the bootstrap., *J Neural Eng* 7(1): 16011.
URL: *http://dx.doi.org/10.1088/1741-2560/7/1/016011*

Gomez, C., Abasolo, D., Poza, J., Fernandez, A. & Hornero, R. (2010). Meg analysis in alzheimer's disease computing approximate entropy for different frequency bands., *Conf Proc IEEE Eng Med Biol Soc* 2010: 2379–2382.
URL: *http://dx.doi.org/10.1109/IEMBS.2010.5627236*

Gross, J., Kujala, J., Hamalainen, M., Timmermann, L., Schnitzler, A. & Salmelin, R. (2001). Dynamic imaging of coherent sources: Studying neural interactions in the human brain., *P Natl Acad Sci USA* 98(2): 694–699.

Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J. & Lounasmaa, O. V. (1993). Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain, *Rev. Mod. Phys.* 65(2): 413–497.

Hund, M., Rezai, A. R., Kronberg, E., Cappell, J., Zonenshayn, M., Ribary, U., Kelly, P. J. & LlinÃąs, R. (1997). Magnetoencephalographic mapping: basic of a new functional risk profile in the selection of patients with cortical brain lesions., *Neurosurgery* 40(5): 936–42; discussion 942–3.

Hymers, M., Prendergast, G., Johnson, S. R. & Green, G. G. R. (2010). Source Stability Index: a novel beamforming based localisation metric., *Neuroimage* 49(2): 1385–1397.

Ince, N. F., Goksu, F., Pellizzer, G., Tewfik, A. & Stephane, M. (2008). Selection of spectro-temporal patterns in multichannel meg with support vector machines for schizophrenia classification., *Conf Proc IEEE Eng Med Biol Soc* 2008: 3554–3557.
URL: *http://dx.doi.org/10.1109/IEMBS.2008.4649973*

Ishii, R., Canuet, L., Kurimoto, R., Ikezawa, K., Aoki, Y., Azechi, M., Takahashi, H., Nakahachi, T., Iwase, M., Kazui, H. & Takeda, M. (2010). Frontal shift of posterior alpha activity is correlated with cognitive impairment in early alzheimer's disease: a magnetoencephalography-beamformer study., *Psychogeriatrics* 10(3): 138–143.
URL: *http://dx.doi.org/10.1111/j.1479-8301.2010.00326.x*

Knake, S., Halgren, E., Shiraishi, H., Hara, K., Hamer, H. M., Grant, P. E., Carr, V. A., Foxe, D., Camposano, S., Busa, E., Witzel, T., HÃd'mÃd'lÃd'inen, M. S., Ahlfors, S. P., Bromfield, E. B., Black, P. M., Bourgeois, B. F., Cole, A. J., Cosgrove, G. R., Dworetzky, B. A., Madsen, J. R., Larsson, P. G., Schomer, D. L., Thiele, E. A., Dale, A. M., Rosen, B. R. & Stufflebeam, S. M. (2006). The value of multichannel meg and eeg in the presurgical evaluation of 70 epilepsy patients., *Epilepsy Res* 69(1): 80–86.
URL: *http://dx.doi.org/10.1016/j.eplepsyres.2006.01.001*

Knowlton, R. C. (2003). Magnetoencephalography: clinical application in epilepsy., *Curr Neurol Neurosci Rep* 3(4): 341–348.

Kotini, A., Anninos, P., Adamopoulos, A. & Prassopoulos, P. (2005). Low-frequency meg activity and mri evaluation in parkinson's disease., *Brain Topogr* 18(1): 59–63.
URL: *http://dx.doi.org/10.1007/s10548-005-7901-4*

Krack, P., Benazzouz, A., Pollak, P., Limousin, P., Piallat, B., Hoffmann, D., Xie, J. & Benabid, A. L. (1998). Treatment of tremor in parkinson's disease by subthalamic nucleus stimulation., *Mov Disord* 13(6): 907–914.
URL: *http://dx.doi.org/10.1002/mds.870130608*

Lefaucheur, J.-P., Drouot, X., Raison, F. V., MÃl'nard-Lefaucheur, I., Cesaro, P. & Nguyen, J.-P. (2004). Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in parkinson's disease., *Clin Neurophysiol* 115(11): 2530–2541.
URL: *http://dx.doi.org/10.1016/j.clinph.2004.05.025*

Litvak, V., Eusebio, A., Jha, A., Oostenveld, R., Barnes, G. R., Penny, W. D., Zrinzo, L., Hariz, M. I., Limousin, P., Friston, K. J. & Brown, P. (2010). Optimized beamforming for simultaneous meg and intracranial local field potential recordings in deep brain stimulation patients., *Neuroimage* 50(4): 1578–1588.
URL: *http://dx.doi.org/10.1016/j.neuroimage.2009.12.115*

Litvak, V., Jha, A., Eusebio, A., Oostenveld, R., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M. I., Friston, K. & Brown, P. (2011). Resting oscillatory cortico-subthalamic connectivity in patients with parkinson's disease., *Brain* 134(Pt 2): 359–374.
URL: *http://dx.doi.org/10.1093/brain/awq332*

Maestü, F., Arrazola, J., Fernändez, A., Simos, P. G., Amo, C., Gil-Gregorio, P., Fernández, S., Papanicolaou, A. & Ortiz, T. (2003). Do cognitive patterns of brain magnetic activity correlate with hippocampal atrophy in alzheimer's disease?, *J Neurol Neurosurg Psychiatry* 74(2): 208–212.

Maestú, F., Fernández, A., Simos, G, P., Gil-Gregorio, P., Amo, C., Rodriguez, R., Arrazola, J. & Ortiz, T. (2001). Spatio-temporal patterns of brain magnetic activity during a memory task in alzheimer's disease., *Neuroreport* 12(18): 3917–3922.

Mally, J. & Stone, T. W. (1999). Improvement in parkinsonian symptoms after repetitive transcranial magnetic stimulation., *J Neurol Sci* 162(2): 179–184.

Martino, J., Honma, S. M., Findlay, A. M., Guggisberg, A. G., Owen, J. P., Kirsch, H. E., Berger, M. S. & Nagarajan, S. S. (2011). Resting functional connectivity in patients with brain tumors in eloquent areas., *Ann Neurol* 69(3): 521–532.
URL: *http://dx.doi.org/10.1002/ana.22167*

Näätänen, R. & Kähkönen, S. (2009). Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (mmn) and its magnetic equivalent mmnm: a review., *Int J Neuropsychopharmacol* 12(1): 125–135.
URL: *http://dx.doi.org/10.1017/S1461145708009322*

Nakasato, N., Levesque, M. F., Barth, D. S., Baumgartner, C., Rogers, R. L. & Sutherling, W. W. (1994). Comparisons of meg, eeg, and ecog source localization in neocortical partial epilepsy in humans., *Electroencephalogr Clin Neurophysiol* 91(3): 171–178.

Obeso, J. A., Rodriguez-Oroz, M. C., Rodriguez, M., Macias, R., Alvarez, L., Guridi, J., Vitek, J. & DeLong, M. R. (2000). Pathophysiologic basis of surgery for parkinson's disease., *Neurology* 55(12 Suppl 6): S7–12.

Osipova, D., Rantanen, K., Ahveninen, J., Ylikoski, R., HÃd'pplÃd', O., Strandberg, T. & Pekkonen, E. (2006). Source estimation of spontaneous meg oscillations in mild cognitive impairment., *Neurosci Lett* 405(1-2): 57–61.
URL: *http://dx.doi.org/10.1016/j.neulet.2006.06.045*

Otsubo, H. & Snead, O. C. (2001). Magnetoencephalography and magnetic source imaging in children., *J Child Neurol* 16(4): 227–235.

Pang, E. W., Drake, J. M., Otsubo, H., Martineau, A., Strantzas, S., Cheyne, D. & Gaetz, W. (2008). Intraoperative confirmation of hand motor area identified preoperatively by magnetoencephalography., *Pediatr Neurosurg* 44(4): 313–317.
URL: *http://dx.doi.org/10.1159/000134923*

Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., Billingsley, R. L., Buchanan, S., Wheless, J., Maggio, V. & Maggio, W. W. (2004). Magnetocephalography: a noninvasive alternative to the wada procedure., *J Neurosurg* 100(5): 867–876.
URL: *http://dx.doi.org/10.3171/jns.2004.100.5.0867*

Parker, M. M. (1947). The clinical utility of electroencephalography in idiopathic epilepsy., *Health Cent J* 1(1): 13–17.

Pekkonen, E., Huotilainen, M., Virtanen, J., NÃd'Ãd'tÃd'nen, R., Ilmoniemi, R. J. & Erkinjuntti, T. (1996). Alzheimer's disease affects parallel processing between the auditory cortices., *Neuroreport* 7(8): 1365–1368.

Pekkonen, E., JÃd'Ãd'skelÃd'inen, L. P., Erkinjuntti, T., Hietanen, M., Huotilainen, M., Ilmoniemi, R. J. & NÃd'Ãd'tÃd'nen, R. (2001). Preserved stimulus deviance detection in alzheimer's disease., *Neuroreport* 12(8): 1649–1652.

Poza, J., Hornero, R., Escudero, J., FernÃąndez, A. & SÃąnchez, C. I. (2008). Regional analysis of spontaneous meg rhythms in patients with alzheimer's disease using spectral entropies., *Ann Biomed Eng* 36(1): 141–152.
URL: *http://dx.doi.org/10.1007/s10439-007-9402-y*

Ray, A. & Bowyer, S. M. (2010). Clinical applications of magnetoencephalography in epilepsy., *Ann Indian Acad Neurol* 13(1): 14–22.
URL: *http://dx.doi.org/10.4103/0972-2327.61271*

Reite, M., Teale, P., Collins, D. & Rojas, D. C. (2010). Schizoaffective disorder - a possible meg auditory evoked field biomarker., *Psychiatry Res* 182(3): 284–286.
URL: *http://dx.doi.org/10.1016/j.pscychresns.2010.02.007*

Roberts, T. P., Ferrari, P., Perry, D., Rowley, H. A. & Berger, M. S. (2000). Presurgical mapping with magnetic source imaging: comparisons with intraoperative findings., *Brain Tumor Pathol* 17(2): 57–64.

Roberts, T. P. L., Khan, S. Y., Rey, M., Monroe, J. F., Cannon, K., Blaskey, L., Woldoff, S., Qasmieh, S., Gandal, M., Schmidt, G. L., Zarnow, D. M., Levy, S. E. & Edgar, J. C.

(2010). Meg detection of delayed auditory evoked responses in autism spectrum disorders: towards an imaging biomarker for autism., *Autism Res* 3(1): 8–18.
URL: *http://dx.doi.org/10.1002/aur.111*

Robinson, S. E. (2004). Localization of event-related activity by SAM(erf)., *Neurol Clin Neurophysiol* p. 109.

Robinson, S. E., Nagarajan, S. S., Mantle, M., Gibbons, V. & Kirsch, H. (2004). Localization of interictal spikes using sam(g2) and dipole fit., *Neurol Clin Neurophysiol* 2004: 74.

Rose, D. F., Sato, S., Ducla-Soares, E. & Kufta, C. V. (1991). Magnetoencephalographic localization of subdural dipoles in a patient with temporal lobe epilepsy., *Epilepsia* 32(5): 635–641.

Rose, D. F., Sato, S., Smith, P. D., Porter, R. J., Theodore, W. H., Friauf, W., Bonner, R. & Jabbari, B. (1987). Localization of magnetic interictal discharges in temporal lobe epilepsy., *Ann Neurol* 22(3): 348–354.
URL: *http://dx.doi.org/10.1002/ana.410220311*

Rossini, P. M., Rossi, S., Babiloni, C. & Polich, J. (2007). Clinical neurophysiology of aging brain: from normal aging to neurodegeneration., *Prog Neurobiol* 83(6): 375–400.
URL: *http://dx.doi.org/10.1016/j.pneurobio.2007.07.010*

Schoffelen, J.-M. & Gross, J. (2009). Source connectivity analysis with meg and eeg., *Hum Brain Mapp* 30(6): 1857–1865.
URL: *http://dx.doi.org/10.1002/hbm.20745*

Schwartz, E. S., Dlugos, D. J., Storm, P. B., Dell, J., Magee, R., Flynn, T. P., Zarnow, D. M., Zimmerman, R. A. & Roberts, T. P. L. (2008). Magnetoencephalography for pediatric epilepsy: how we do it., *AJNR Am J Neuroradiol* 29(5): 832–837.
URL: *http://dx.doi.org/10.3174/ajnr.A1029*

Shah, Y., Tangalos, E. G. & Petersen, R. C. (2000). Mild cognitive impairment. when is it a precursor to alzheimer's disease?, *Geriatrics* 55(9): 62, 65–62, 68.

Simos, P. G., Breier, J. I., Zouridakis, G. & Papanicolaou, A. C. (1998). Assessment of functional cerebral laterality for language using magnetoencephalography., *J Clin Neurophysiol* 15(4): 364–372.

Simos, P. G., Papanicolaou, A. C., Breier, J. I., Fletcher, J. M., Wheless, J. W., Maggio, W. W., Gormley, W., Constantinou, J. E. & Kramer, L. (2000). Insights into brain function and neural plasticity using magnetic source imaging., *J Clin Neurophysiol* 17(2): 143–162.

Stam, C. J. (2010). Use of magnetoencephalography (meg) to study functional brain networks in neurodegenerative disorders., *J Neurol Sci* 289(1-2): 128–134.
URL: *http://dx.doi.org/10.1016/j.jns.2009.08.028*

Stoffers, D., Bosboom, J. L. W., Deijen, J. B., Wolters, E. C., Berendse, H. W. & Stam, C. J. (2007). Slowing of oscillatory brain activity is a stable characteristic of parkinson's disease without dementia., *Brain* 130(Pt 7): 1847–1860.
URL: *http://dx.doi.org/10.1093/brain/awm034*

Stoffers, D., Bosboom, J. L. W., Deijen, J. B., Wolters, E. C., Stam, C. J. & Berendse, H. W. (2008). Increased cortico-cortical functional connectivity in early-stage parkinson's disease: an meg study., *Neuroimage* 41(2): 212–222.
URL: *http://dx.doi.org/10.1016/j.neuroimage.2008.02.027*

Timmermann, L., Florin, E. & Reck, C. (2007). Pathological cerebral oscillatory activity in parkinson's disease: a critical review on methods, data and hypotheses., *Expert Rev Med Devices* 4(5): 651–661.
URL: *http://dx.doi.org/10.1586/17434440.4.5.651*

Timmermann, L., Gross, J., Dirks, M., Volkmann, J., Freund, H.-J. & Schnitzler, A. (2003). The cerebral oscillatory network of parkinsonian resting tremor., *Brain* 126(Pt 1): 199–212.

Tovar-Spinoza, Z. S., Ochi, A., Rutka, J. T., Go, C. & Otsubo, H. (2008). The role of magnetoencephalography in epilepsy surgery., *Neurosurg Focus* 25(3): E16.
URL: *http://dx.doi.org/10.3171/FOC/2008/25/9/E16*

Uhlhaas, P. J., Haenschel, C., NikoliÄĞ, D. & Singer, W. (2008). The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia., *Schizophr Bull* 34(5): 927–943.
URL: *http://dx.doi.org/10.1093/schbul/sbn062*

Urrestarazu, E., Chander, R., Dubeau, F. & Gotman, J. (2007). Interictal high-frequency oscillations (100-500 hz) in the intracerebral eeg of epileptic patients., *Brain* 130(Pt 9): 2354–2366.
URL: *http://dx.doi.org/10.1093/brain/awm149*

Urrestarazu, E., Jirsch, J. D., LeVan, P., Hall, J., Avoli, M., Dubeau, F. & Gotman, J. (2006). High-frequency intracerebral eeg activity (100-500 hz) following interictal spikes., *Epilepsia* 47(9): 1465–1476.
URL: *http://dx.doi.org/10.1111/j.1528-1167.2006.00618.x*

Van Veen, B. D., van Drongelen, W., Yuchtman, M. & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering, *IEEE T Bio-med Eng* 44(9): 867–880.

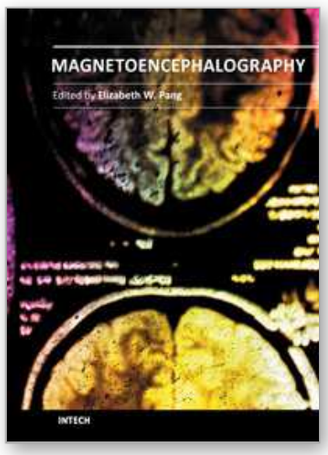
Volkmann, J., Joliot, M., Mogilner, A., Ioannides, A. A., Lado, F., Fazzini, E., Ribary, U. & LlinÃąs, R. (1996). Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography., *Neurology* 46(5): 1359–1370.

Wada, J. & Rasmussen, T. (2007). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960., *J Neurosurg* 106(6): 1117–1133.
URL: *http://dx.doi.org/10.3171/jns.2007.106.6.1117*

Wu, A. D., Fregni, F., Simon, D. K., Deblieck, C. & Pascual-Leone, A. (2008). Noninvasive brain stimulation for parkinson's disease and dystonia., *Neurotherapeutics* 5(2): 345–361.
URL: *http://dx.doi.org/10.1016/j.nurt.2008.02.002*

Xiang, J., Liu, Y., Wang, Y., Kirtman, E. G., Kotecha, R., Chen, Y., Huo, X., Fujiwara, H., Hemasilpin, N., Lee, K., Mangano, F. T., Leach, J., Jones, B., DeGrauw, T. & Rose, D. (2009). Frequency and spatial characteristics of high-frequency neuromagnetic signals in childhood epilepsy., *Epileptic Disord* 11(2): 113–125.
URL: *http://dx.doi.org/10.1684/epd.2009.0253*

Xiang, J., Wang, Y., Chen, Y., Liu, Y., Kotecha, R., Huo, X., Rose, D. F., Fujiwara, H., Hemasilpin, N., Lee, K., Mangano, F. T., Jones, B. & DeGrauw, T. (2010). Noninvasive localization of epileptogenic zones with ictal high-frequency neuromagnetic signals., *J Neurosurg Pediatr* 5(1): 113–122.
URL: *http://dx.doi.org/10.3171/2009.8.PEDS09345*



Magnetoencephalography

Edited by Dr. Elizabeth Pang

ISBN 978-953-307-255-5
Hard cover, 252 pages
Publisher InTech
Published online 30, November, 2011
Published in print edition November, 2011

This is a practical book on MEG that covers a wide range of topics. The book begins with a series of reviews on the use of MEG for clinical applications, the study of cognitive functions in various diseases, and one chapter focusing specifically on studies of memory with MEG. There are sections with chapters that describe source localization issues, the use of beamformers and dipole source methods, as well as phase-based analyses, and a step-by-step guide to using dipoles for epilepsy spike analyses. The book ends with a section describing new innovations in MEG systems, namely an on-line real-time MEG data acquisition system, novel applications for MEG research, and a proposal for a helium re-circulation system. With such breadth of topics, there will be a chapter that is of interest to every MEG researcher or clinician.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen